SUB A12 cont regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences.

98. (New) A method for introducing homologous or heterologous nucleotide sequences into cells in an animal or cultured cells, said method comprising infecting the cells with recombinant retroviruses produced by the producer cell line of Claim 97.

99. (New) The method according to Claim 98, wherein the nucleotide sequences are selected from the group consisting of genes or parts of genes encoding for proteins, regulatory sequences and promoters and combinations thereof.

GS cont

100. (New) A recombinant retroviral particle comprising the retroviral vector according to Claim 79.

101. (New) The retroviral vector according to Claim 79, wherein said promoter is target cell specific in its expression.

REMARKS

Claim Amendments

Claims 1, 17, and 28 have been amended to recite a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences. Support for the amendments can be found, for example, in Examples 1 and 2 of the specification,

which exemplify the claimed retroviral vector using a MMTV promoter in a BAG MLV vector and a WAP promoter in a BAG MLV vector.

New Claims 33-55, which are directed to a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a promoter from a cellular gene is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences, have been added. Support for the new claims can be found, for example, in Examples 1 and 2 of the specification, which exemplify the claimed retroviral vector using a WAP promoter in a BAG MLV vector.

New Claims 56-78, which are directed to a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous retroviral promoter which is derived from a promoter of a retrovirus other than a retrovirus upon which the retroviral vector is based or other than a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences, have been added. Support for the new claims can be found, for example, in Examples 1 and 2 of the specification, which exemplify the claimed retroviral vector using a MMTV promoter in a BAG MLV vector.

New Claims 79-101, which are directed to a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a retroviral promoter is inserted, said promoter

regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences, have been added. Support for the new claims can be found, for example, in Examples 1 and 2 of the specification, which exemplify the claimed retroviral vector using a WAP promoter in a BAG MLV vector.

<u>Rejection of Claims 1, 5, 7, 9-26, 28, 29, 31 and 32 under 35 U.S.C. §112, first paragraph</u>

Claims 1, 5, 7, 9-26, 31 and 32 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), a the time the application was filed, had possession of the claimed invention" (Office Action, page 1). The Examiner states that a "review of the specification does not reveal subject matter that supports the amendment" and "[w]hile the specification provides an example of insertion of a promoters from a cellular gene, it does not provide support for the genus of promoters that are not derived from a retroviral vector, or for the genus of promoters that are not from a retrovirus that is related to the retroviral vector" (Office Action, pages 1-2).

Applicants respectfully disagree. There is no *in haec verba* requirement for new or added claim language and such language can be supported in the specification through express, implicit or inherent disclosure (MPEP 2163).

In the specification as filed, Applicants describe the insertion of the mouse mammary tumor virus (MMTV) promoter, a retroviral promoter, into the murine leukemia virus (MLV) retroviral vector, BAG, and the insertion of the Whey Acidic protein (WAP) promoter, a cellular gene promoter, into the MLV BAG vector (specification, Example 1). Applicants also demonstrate that the β-gal gene, which is in the body of the BAG retroviral vector, was under transcriptional control of the MMTV promoter and the WAP promoter after infection *in vitro* and *in vivo* (specification, page 21, line 1 - page 24, line 2). Neither the MMTV promoter nor the WAP promoter are promoters derived from the MLV BAG vector. Furthermore, the MMTV retroviral promoter is from a retrovirus that is not related to MLV.

Thus, Applicants have provided two working examples of a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding

sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences. Clearly, in the specification as filed, Applicants have subject matter that supports the amendment.

The subject specification as filed clearly indicates that Applicant had possession of the claimed invention at the time the application was filed.

Rejection of Claims 1, 5, 7, 9-26, 28, 29, 31 and 32 under 35 U.S.C. §112, second paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31 and 32 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 2).

The Examiner states that Claims 1, 5, 7, 9-26, 31 and 32 "are indefinite for recitation of the phrase 'a heterologous promoter which is not derived from the retrovirus of a related retrovirus upon which the retroviral vector is based' because the metes and bounds of the claimed promoter are unclear" (Office Action, page 2).

Applicants respectfully disagree. The claims have been amended to indicate that the heterologous promoter is a promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences. The language clearly indicates that the heterologous promoter has to be a promoter that does not naturally occur in the retroviral vector and that such a promoter regulates, after infection of a target cell, expression of the one or more sequences selected from coding and non-coding sequences, which is measured using routine skills as described in the subject application.

The Examiner states that Claim 7 "is indefinite because it is limited in the preamble to a vector comprising a promoter, but the promoter is selected from a group that includes promoters and regulatory elements, rather than a group of promoters" (Office Action, page 2).

Claim 7 has been amended to more clearly indicate that the group includes promoters.

Rejection of Claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31 and 32 under 35 U.S.C. §103(a)

Claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31 and 32 under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al." (Office Action, page 5). It is the Examiner's opinion that:

> [i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning sites of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector (Office Action, page 4).

Applicants respectfully disagree. As pointed out above, in order to more clearly distinguish Applicant's claimed invention, the claims have been amended to indicate that the partially deleted U3 region includes a polylinker sequence containing a heterologous promoter other than a promoter from a retrovirus upon which the retroviral vector is based or a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences. Applicants have also added new Claims 33-101, which clearly distinguish over the cited art. Applicants understand that the Examiner may have problems with Applicants' proposed claims and respectfully invite the Examiner to suggest other possible claim language which he may find acceptable to distinguish Applicants' claimed invention over the cited art.

Couture *et al.* replaced the U3 region of Mo-MLV by the corresponding region from five related murine retroviruses, AKV, HaMSV, MPSV, SL3-3 and Xeno. A characteristic feature of these retroviruses is that they are closely related in being subtypes of murine retroviruses. For example, it is believed that SL3-3 MLV is derived from AKV which in turn is an endogenous MLV of the AKR strain (see, for example, Ethelberg *et al., J. Virol.,*

71:1196-1206 (1997) which is being filed concurrently herewith as the Exhibit; in particular see page 1196, right column, 2nd paragraph of Ethelberg *et al.*). Subtypes of organism generally have their genomes in common (and this includes the U3 region including, in turn, the promoter) which are highly conserved and only differ in small nucleotide variations. As indicated in Ethelberg *et al.*, particularly the U3 region of "closely related MLV isolates" and subtypes of murine retroviruses, respectively, is highly conserved. For example, the NF1 sites (also included in the U3 region) of MLV and SL3-3 MLV are identical except for a 1 bp difference (Ethelberg *et al.*, page 1024, left column, last paragraph through right column, 1st paragraph). Mo-MLV and SL3-3 are further similar in the region known as the enhancer framework encompassing the core, Ets, NF1 and the overlapping GR and ALF1 sites which are all included in the U3 region (Ethelberg *et al.*, page 11965, right column, 2nd paragraph). Thus, replacement of the U3 region of the Mo-MLV with highly conserved, and thus, nearly identical U3 regions of a closely related murine retroviral subtypes, as described in the Couture *et al.* reference, are not encompassed by Applicants' claimed invention, particularly as amended.

Faustinella *et al.* teach a modified MLV vector comprising a partially deleted 3' U3 region which is substituted by either a luciferase reporter gene directly linked to a rous sarcoma virus promoter or a hygromycin resistance gene directly linked to a herpes simplex thymidine kinase promoter. Alternatively, Faustinella *et al.* teach that the gene directly linked to the promoter can be subcloned into the body of the vector. Faustinella *et al.* do not teach or even suggest that the promoter in the 3' U3 region of the MLV can be replaced with a heterologous promoter which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based, for the purpose of directing expression of a coding sequence in the body of the vector (*i.e.*, directing the expression of a coding sequence which is not directly linked to the heterologous promoter in the retroviral vector).

In the previously filed Amendments, Applicants provide a detailed discussion of the state of the art at the time of Applicants' invention, which indicates why one of skill in the art would find that the heterologous promoter in the U3 region of Applicants' claimed retroviral vectors would regulate, after infection, expression of a coding sequence in the body of the vector. However, the Examiner has not responded to the majority of these discussions. The

Examiner addresses the teaching in the Junker *et al.* reference which was filed in support of one of Applicants' points (i.e., that one of skill in the art would expect genetic rearrangement to occur during reverse transcription of Applicants' vectors). In particular, the Examiner states that:

> applicants state that Junker et al, provided in the amendment received 10 May 1999, shows that insertion of heterologous promoters results in rearrangements and unstable vectors and teaches away from use of heterologous promoters inserted in the LTR of a retroviral vector. However, Junker et al. concludes on page 643 that the rearrangements observed are due to the presence of short direct 22 base repeats that flank the insertion within each LTR in the vector used by Junker et al. Therefore, Junker et al. shows that direct repeats within an LTR can result in instability, but does not show that large scale repeats such as the LTR normally present in retroviruses or the inserted LTR of Couture et al. would lead to instability (Office Action, page 8).

Applicants respectfully disagree. Junker *et al.* teach that the direct repeats are part of a combined effect and only one mechanism that is possibly responsible for the observed deletions (Junker *et al.*, page 644, column 1).

Applicants respectfully request that the Examiner address Applicants' additional discussions regarding the state of the art at the time of Applicants' invention in light of the teachings in the Junker *et al.* reference. The discussion is again included herein.

According to the general state of the art, retroviral vector systems (DNA) comprise identical 5' and 3' LTRs, both having the structure U3-R-U5. For transfer of these DNA constructs into target cells the DNA must at first be transcribed into RNA. Although both LTRs of the DNA constructs are identical in structure, they are distinct in function. The 5' LTR directs initiation of transcription at the R-region of the 5' LTR, while cleavage and polyadenylation of the transcript occurs at the R region of the 3' LTR (specification, Figure 3). However, both R regions, that of the 5' LTR as well as the 3' LTR, are identical and comprise polyadenylation signals. Therefore, the questions of interest is: Why does transcription not stop at the end of the R region of the 5' LTR but moves on to identical sequences of the R region of the 3' LTR and stops at the end of the R region of the 3' LTR?

To explain the apparent inability of the 5' LTR to function efficiently as a poly(A) addition site it is presumed that sequences upstream of the R region, namely in the U3 region, allow transcriptional read-through of the 5' R region. Accordingly, when developing retroviral

vector constructs with an altered U3 region, as disclosed by Faustinella *et al.* and Couture *et al.*, as well as described in the present invention, only the U3 region of the 3' LTR is altered, while the normal 5' U3 region is maintained to ensure transcriptional read-through of the 5' R region during generation of recombinant retroviral particles. However, the generated RNA only contains the altered 3' U3 region.

In the infected target cell the RNA is reverse transcribed into DNA. During reverse transcription, the altered 3' U3 region is duplicated into the 5' LTR. When comparing the constructs developed by Faustinella *et al.* and Couture *et al.* with the construct according to the present invention you'll find the following:

1. According to Couture *et al.* the U3 region upstream of the 5' R region is changed by complete replacement of the wild type region by corresponding regions of closely related retroviruses and subtypes of the retroviruses, respectively, driving expression of the genes inserted into the body of the vector (Figure 1).

2. According to Faustinella *et al.* the partially deleted U3 region upstream of the 5' R region always comprises a promoter and a gene; a promoter and a gene can additionally be inserted into the body of the vector (Figure 2).

After integration into the host cell genome, transcription of the genes is expected in the Faustinella *et al.* and the Couture *et al.* constructs, but not in the constructs according to the present invention.

In case of the Faustinella *et al.* construct, a gene and a promoter are always directly linked when inserted into the 5' U3 region and when inserted into the body of the vector. Accordingly, when using such "cassettes" the problem of transcriptional read through of the 5' R region is circumvented. Since transcription of each gene is independently driven by an "own", directly linked promoter, regulatory elements presumed to be inserted into the normal 5' U3 region to allow transcriptional read-through of the 5' R region and being deleted in the now altered or completely deleted 5' U3 region are without relevance, because a transcriptional read-through of the 5' R region is not demanded. In the Faustinella *et al.*

consrtuct, transcription of the genes is independent from sequences upstream of the R region of the original retroviral vector; the vector is only used as a shuttle for transferring expression-cassettes into the genome of a target cell.

In contrast, according to the present invention, transcription of foreign genes inserted into the body of the vector (without being directly linked to a promoter) is dependent from a heterologous promoter inserted into the 5' U3 region. In this case, transcriptional read-through of the 5' R region for expression of the genes is undoubtably demanded. Since the original 5' U3 region is partially deleted according to the examples even up to the inverted repeats - it is expected that original retroviral vector elements allowing transcriptional read-through of the unchanged 5' R region of the retroviral vector are also deleted. Thus, when inserting a heterologous promoter, which is not directly linked to a gene, into a partially deleted U3 region it was expected that initiation of transcription might, if at all, occur, but it was not at all expected that a transcriptional read-through of the 5' R region and, thus, a transcription of foreign genes would still occur. The finding that foreign genes inserted into the body of the vector are expressed and that, thus, a transcriptional read-through of the 5' R region still works must therefore be regarded as a surprising result in view of disclosure of Faustinella *et al.*

The same is true when considering disclosure of Couture *et al.* According to this document the 5' U3 region is only replaced by a corresponding region of closely related murine retroviruses. Accordingly, the 5' U3 region remains nearly unchanged. Thus, in view of the above explanations, it is not surprising that 5' U3 regions in which only closely related regions and promoters are exchanged still allow transcriptional read-through of the 5' R region. A skilled practitioner, being aware of the transcriptional regulation of genes inserted into the body of the vector and which are to be expressed in the host cell, would have only considered, if at all, to replace the promoter inserted into the U3 region by a closely related promoter. In view of the above explanations the skilled practitioner would not have considered to insert into a partially deleted U3 region a heterologous promoter not derived from the same retrovirus or from subtypes of the retrovirus upon which the retroviral vector is based, because, a the time fo Applicants' invention, the practitioner would have expected that a transcriptional read-through of the 5' R region, and thus, expression of genes would not occur. However, the heterologous genes included in the body of the vector are, in fact,

expressed by the heterologous promoter inserted in the partially deleted U3 region. Accordingly, the technical teaching of the present invention as now claimed must be regarded as non-obvious when considering disclosure of Couture *et al.* in view of Faustinella *et al.*

A further argument is based on the following finding which was discussed briefly above. In the scientific literature it is reported that genetic rearrangement occurs during reverse transcription, especially when heterologous elements are inserted into the U3 region of the LTR (see Junker *et al.*). Such genetic rearrangement are without relevance to the Couture *et al.* construct, because elements, in particular heterologous elements, are not inserted into the U3 region. As already mentioned above, in the Couture *et al.* construct the U3 region is replaced by a U3 region of closely related viruses. In the Faustinella *et al.* construct, genetic rearrangement might occur, but will also not be relevant, because promoter plus gene are always directly linked. Therefore, it is very unlikely that this construct is rearranged during reverse transcription in such a way that the promoter no longer drives gene expression. However, this was expected with Applicants' claimed vectors. With Applicants' claimed vectors, a heterologous promoter, and thus, a heterologous element is inserted into the U3 region. Accordingly, genetic rearrangement would be expected during reverse transcription. Since the promoter additionally drives gene expression of genes not directly linked to the promoter, but inserted into the body of the vector, it would also be expected that genetic rearrangement results in constructs in which the promoter is no longer upstream of the genes. Thus, it was expected that gene expression would not occur after integration of the construct into the host cell genome. In contrast, it was surprising that the vector according to the present invention remains stable and that foreign genes inserted into the body of the vector are expressed.

Clearly, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claims 13 and 14 under 35 U.S.C. §103(a)

Claims 13 and 14 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31 and 32 above, and further as evidenced by Miller et al. and Panganiban et al."

(Office Action, page 4). The Examiner states that Couture *et al.* in view of Faustinella *et al.* "do not explicitly show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses", but note that Couture *et al.* show that "their vectors are derivatives of the vectors of Miller et al. (Office Action, pages 4-5). The Examiner cites Miller *et al.* as showing that "their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent virus"; and Panganiban *et al.* as showing that "the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus" (Office Action, page 5).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Miller *et al.* and Panganiban *et al.* do not provide the teaching lacking in Couture *et al.* and Faustinella *et al.* references. As discussed in the previously filed amendments, Miller *et al.* designed "a set of retroviral vectors which facilitate cDNA transfer and expression" (Miller *et al.*, page 986, column 3), one of which is the LNSX retroviral vector used by Couture *et al.* to generate their vectors. Panganiban *et al.* ('84) mutagenized cloned spleen necrosis virus and showed that the 3' end of the *pol* gene of the spleen necrosis virus encodes a polypeptide required for DNA integration through interaction with the *att* site. Miller *et al.* nor Panganiban *et al.* do not teach or even suggest a retroviral vector wherein the U3 region comprises a heterologous promoter *which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based* and which regulates expression of a coding sequence inserted into the body of the vector after infection of the target cell. Furthermore, Miller *et al.* and Panganiban *et al.* do not provide a reasonable expectation that doing so would result in expression of the gene.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.*, Miller *et al.* and Panganiban *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claim 10 under 35 U.S.C. §103(a)

Claim 10 is rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31

and 32 above, and further in view of Price et al." (Office Action, page 8). The Examiner states that Couture *et al.* in view of Faustinella *et al.* "does not show a vector derived from a BAG vector" (Office Action, page 5). The Examiner states that Price *et al.* show "a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector" (Office Action, page 5).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Price *et al.* do not provide the teaching lacking in Couture *et al.* and Faustinella *et al.* references. As discussed in the previously filed amendments, Price *et al.* applied a β-gal-transducing vector, BAG, "to the study of neural lineage *in vivo* and in culture" and were able to mark cells in both cases (Price *et al.*, page 158, column 2). In particular, Price *et al.* inserted the β-gal gene, the SV40 early promoter and the Tn5 *neo* gene into the body of the pDOL vector, which is derived from the Moloney murine leukemia virus (Mo-MuLV), and used the vector as a cell-lineage marking system applicable to the vertebrate nervous system. There is clearly no discussion in the Price *et al.* reference regarding the manipulation of the U3 region of the pDOL vector for any purpose.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.*, and Price *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claims 15, 20, 21 and 26 under 35 U.S.C. §103(a)

Claims 15, 20, 21 and 26 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31 and 32 above, and further in view of Longmore et al. and Kay et al." (Office Action, page 6). The Examiner states that Couture *et al.* in view of Faustinella *et al.* "does not show use of retroviral vectors in an animal" (Office Action, page 6). The Examiner states that Longmore *et al.* show that "mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes"; and that Kay *et al.* show that "hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment" (Office Action, page 6).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Longmore *et al.* and Kay *et al.* do not provide the teaching lacking in Couture *et al.* and Faustinella *et al.* references. As discussed in the previously filed amendments, Longmore *et al.* infected mice with a recombinant spleen focus-forming retrovirus (SFFV) expressing an oncogenic erythropoietin (Epo) receptor (EpoR) and showed a relationship between erythropoiesis and thrombopoiesis at the level of the Epo-EpoR signalling pathway. In addition, Longmore *et al.* teach that the SFV-based vectors "may be excellent vehicles for the introduction of genes into multipotent, hematopoietic progenitors, in vitro" (Longmore *et al.*, abstract). Using an amphotropic retroviral vector that encoded the canine factor IX complementary DNA, Kay *et al.* determined that a method for hepatic gene transfer *in vivo* by the direct infusion of recombinant retroviral vectors into the portal vasculature of a hemophilia B dog model, which results in the persistent expression of exogenous genes, may be feasible for the treatment of hemophilia B patients. There is no discussion in the Longmore *et al.* or Kay *et al.* references regarding the manipulation of the U3 region of their retroviral vectors for any purpose.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.*, Longmore *et al.* and Kay *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

<u>Rejection of Claim 7 under 35 U.S.C. §103(a)</u>

Claim 7 is rejected under 35 U.S.C. §103(a) "as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 29, 29, 31 and 32 above, and further in view of Mee et al." (Office Action, page 8). The Examiner states that Couture *et al.* in view of Faustinella *et al.* "does not show the claimed promoter or regulatory elements" (Office Action, page 10). The Examiner states that Mee *et al.* show "a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone" and that "their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types" (Office Action, page 7).

Applicants respectfully disagree. As pointed out above, the combined teachings of Couture *et al.* and Faustinella *et al.* do not render obvious Applicants' claimed invention. Mee

et al. do not provide the teaching lacking in Couture *et al.* and Faustinella *et al.* references. As discussed in the previously filed amendments, Mee *et al.* teach the construction and properties of a self-inactivating (SIN) retroviral vector containing a hormonally regulated transcriptional element. In particular, Mee *et al.* disabled the 3' LTR of a retroviral vector and cloned the HRE inducible promoter of the MMTV and the *aph* gene directly between the LTRs of the provirus, *i.e.,* into the body of the vector (Mee *et al.*, pages 289-290). Mee *et al.* do not teach insertion of a heterologous promoter into a partially deleted U3 region of a retroviral vector.

Clearly, the combined teachings of Couture *et al.*, Faustinella *et al.* and Mee *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,
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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,
   d) a 5' long terminal repeat region of the structure U3-R-U5;
   e) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and
   f) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter [which is not derived from the] other than a promoter from a retrovirus upon which the retroviral vector is based or [a related] a promoter from a subtype of the retrovirus upon which the retroviral vector is based is inserted, said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences.

7. (Three times amended) The retroviral vector according to Claim 31, wherein said promoter is selected from the group consisting of: a Whey Acidic Protein specific [regulatory elements and] promoter[s], a Mouse Mammary Tumor Virus specific [regulatory elements and] promoter[s], β-lactoglobulin and casein specific [regulatory elements and] promoters, a pancreas specific [regulatory elements and] promoter[s], lymphocyte specific [regulatory elements and] promoter[s], a Mouse Mammary Tumor Virus specific [regulatory elements and] promoter[s] conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland, and combinations thereof.

17. (Three times amended) A retroviral vector kit comprising:

a retroviral vector which undergoes promoter conversion comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter is inserted, wherein said promoter is [not] derived from [the] a promoter other than a promoter from a retrovirus upon which the retroviral vector is based or [a related] a promoter from a subtype of the retrovirus upon which the retroviral vector is based and said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences; and

a packaging cell line harboring at least one retroviral or recombinant retroviral construct coding for proteins required for said retroviral vector to be packaged.

28. (Three times amended) A producer cell line producing a retroviral particle, the producer cell comprising a retroviral vector and a DNA construct coding for proteins required for the retroviral vector to be packaged, said retroviral vector comprising in 5' to 3' order, a) a 5' long terminal repeat region of the structure U3-R-U5; b) one or more sequences selected from coding and non-coding sequences, said sequences being inserted into the body of the vector; and c) a 3' long terminal repeat region comprising a partially deleted U3 region wherein in said partially deleted U3 region a polylinker sequence containing a heterologous promoter is inserted, wherein said promoter is [not derived from the] other than a promoter from a retrovirus upon which the retroviral vector is based or [a related] a promoter from a subtype of the retrovirus upon which the retroviral vector is based and said promoter regulating, after infection of a target cell, expression of said one or more sequences selected from coding and non-coding sequences.